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NUTRITION REVIEWS

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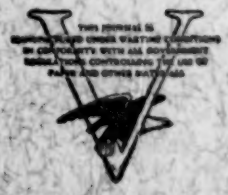

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NUTRITION REVIEWS

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THE FOOD CLINIC IN NUTRITION

In recent years federal, state, and city organizations have been concerning themselves with the betterment of the nutritional status of the people. This movement was crystallized in the Proceedings of the National Nutrition Conference for Defense, called by the President of the United States in 1941, "to discuss the problems of nutrition for defense and to formulate recommendations for a national program of action." As reported in the Proceedings of the Conference, it was recommended, in the section on "Public Health and Medical Aspects of Nutrition," that "the establishment of therapeutic diet clinics in connection with hospitals and medical centers be actively promoted," and that "additional training in nutrition be given in schools of medicine and public health with special attention to teaching the economic aspects of adequate nutrition."

During and following the last war many food clinics pioneered in service to the ambulatory patient and these are destined to play an even more important part in the postwar period. Millions of ambulatory patients need dietary instruction. The recognition of this need led in part to the establishment of the first food clinic at the Boston Dispensary twenty-five years ago. Rooted deeply in the clinic was the belief that the newer knowledge of nutrition could be so interpreted to the patient that its application in his life would make for the improvement of health and the betterment of living.

It has been found through the experience of years that the Food Clinic should be an integral part of the Medical Clinic and in administrative matters should function like every other clinic, caring for the problems in its own field and affiliating with other clinics or departments when there is need for mutual service.

After a complete physical examination, inclusive of laboratory findings, the physician refers the patient to the Food Clinic. The record of this examination, together with the physician's food prescription, serves as a basis for the dietitian in planning a diet. The food order for the patient is written in terms of total amounts of food for the day with alternatives in kinds and amounts for variation. Menus and recipes are supplied if desired.

The establishment of the Food Clinic required new technics and procedures which would make it possible for the ambulatory patient to carry out his food prescription between visits to the clinic. To help the patient it was necessary to know the patient. The primary step toward this end was the formulation of a nutritional history which would give the dietitian as complete a picture as possible of the patient and his environment. Dr. Francis W. Peabody has said in "Doctor and Patient," "What is spoken of as a clinical picture is not just a photograph of a man sick in bed; it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes and fears."

This belief has been echoed by every food clinic dietitian. In conference with the patient the dietitian encourages him to talk freely of himself—his habits, tastes, occupation, family, work, income, hygiene, both mental and physical—every factor in the home, community, school, and industry that may affect the success of food treatment. Behavior in relation to food is often a matter of interplay between the physical and emotional life. The motive may be hidden in a condition or a combination of circumstances seemingly unrelated or only indirectly related to food and consciously or unconsciously guarded by defensive attitudes that are difficult to penetrate. The necessaries

of life—food, shelter, clothing, and savings—are closely interrelated in their demands upon the income, and it requires careful planning to keep the outlay for them in proper ratio. The problem of good nutrition for the wage earner is closely related to the prevailing conditions in labor and industry. It is essential in dietetic treatment to be aware of the extent to which these demands, singly or in combination, may prevent the fulfillment of the body's need for sufficient food. Primary needs cannot be satisfied when the income is below the minimum level of the cost of living. Under such conditions one or more of these needs will inevitably fall below good health standards.

Constant consideration must be given to promoting a friendly relationship between dietitian and patient, always with the ultimate goal of making the teaching more effective. The room in which the Food Clinic is held should be as attractive as possible. Pictures and objects that represent the cultural life of many nationalities remind the foreign born of his native land, encourage friendliness, and are a distinct aid to treatment. Once the confidence of the patient is gained, he becomes interested in the plan of food treatment and is loyal to it.

It was the original purpose of the Food Clinic to assist in the medical treatment of the ambulatory patient by interpreting to him the physician's food prescription. As time went on it was possible to make food treatment more effective by teaching the patient the relation of food to the body, thus helping him to understand the reason for his diet. Simple educational material, which employed visualization wherever possible, accomplished this purpose. Wax food models show the patient the kinds and amounts of foods his diet allows, obviating the burden of weighing food. Printed and mimeographed leaflets, in terms that are easily understood, are given the patient so that he may review at home the information given in the clinic. Picture sheets that supply scientific information are invaluable, especially to those for whom printed material is difficult. Exhibits, too, are an effective means of disseminating knowledge of the principles and important facts of nutrition. The technics employed in the teaching of children in the clinic also are becoming an integral part of the educational system in public and private schools.

The demands for training in applied dietetics have led to the formation of classes. Medical students, as well as practicing physicians, meet in the clinic and learn the dietetic treatment of the patient in the office, hospital, and clinic. Through the Food Clinic social workers increase their understanding of the principles of diet therapy and the influence of related environmental factors and are better able to help the patient make the best possible social and economic adjustments to his diet. The student in home economics or applied dietetics, already familiar with the principles of the science of nutrition, is given experience in applying these principles to the treatment of an individual patient in terms of particular needs. Teachers and public health workers deeply concerned in community health, and serving as interpreters of scientific findings, become aware of the great need for guidance in teaching the relation of food to the body. The nurse realizes the importance of a knowledge of nutrition and finds the clinic a means of making practical application of this knowledge.

It became evident that a special type of training was needed for both the dietitian in the outpatient clinic and the nutritionist in the community. The technic and the approach to the ambulatory patient differs in many ways from hospital practice. Therefore the training which the Food Clinic offers to the student dietitian fosters a knowledge and understanding of the many problems confronting the ambulatory patient, whether medical, socio-economic, or mental, and the ability to carry out the primary purpose of the Food Clinic which is

to assist the physician effectively when food treatment is part of medical treatment. This type of training also gives special emphasis to the nutritional education of the layman, thus enabling the student dietitian to contribute practical service to the community. An important phase of this service is the teaching and interpretation of projects within the government's nutritional program, such as the current rationing program.

The Food Clinic serves the community by participating in extramural meetings, lectures, and conferences, and also serves as a teaching center for the public. Here the public—worker, student, or lay person, professional or nonprofessional—can find interpretation and evaluation of the mass of nutritional material which comes through newspapers, magazines, and radio.

Dr. Russell M. Wilder, in an article entitled "The Teaching of Nutrition in Schools of Medicine" (*J. Assn. Med. Colleges* **18,** *145 (1943)*) wrote: "At present there are few physicians, dentists or public health officers who are qualified to take an authoritative position in the field of nutrition, but the need for them is very great. This situation urgently requires remedies in each of the three following ways: Better training in nutrition for medical, dental and public health students; extensive postgraduate courses in nutrition; broad and extensive training of numbers of physicians and dentists to provide the necessary medical guidance for the many professional and nonprofessional persons who are concerned with the nutritional needs of the people." To meet this need he recommended the establishment of nutrition clinics "in association with the professional schools and to provide facilities for research and advanced training in nutrition." He further stated: "The nutrition clinic could be made a place for intensive training for certain selected students." The realization of this hope is not too distant, for the success of the present clinics gives promise that every outpatient department will have a Food Clinic and every teaching hospital will have adequate facilities for teaching applied nutrition.

The demands for the services of a Food Clinic are constantly increasing. In its scope, the Food Clinic not only encompasses the treatment of the ambulatory patient but has developed into a vital teaching center where all groups in the medical and allied professions are given ample opportunity to practice applied nutrition. It has become a moving force behind the constant endeavor to improve the nutritional status of the people, and it looks beyond the present conflict to a world in which the health and stamina of the people will far transcend their present level.

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INOSITOL

Few substances that are available as pure chemicals have presented such a confusing picture in nutrition as has inositol. Not only have claims for an essential role of inositol been denied, but some workers believe that its inclusion in the diet is actually injurious. In 1928 Eastcott (*J. Physical Chem.* **32,** *1094 (1928)*) showed that inositol was required for the growth of certain yeasts. This function of inositol allows the use of microbiologic methods for its determination, and by this method Williams and co-workers (*Univ. of Texas Publ. no.* **4237** *(1942)*) have extended previous data on the distribution of inositol. The wide distribution in animal and plant tissues in rather large amounts presupposes an important physiologic function. It is of interest that the nucleated red blood cells of birds and reptiles contain considerable inositol as the phosphate ester, while

non-nucleated cells do not (Rapoport, *J. Biol. Chem.* **135,** *403 (1940)*).

In studies of purified diets for mice, Woolley (*J. Biol. Chem.* **139,** *29 (1941)*) showed that a severe alopecia developed in this species which could be cured or prevented by inositol. However, the picture was confusing since alopecia also developed on rations low in pantothenic acid and spontaneous cures of inositol deficiency appeared frequently (Woolley, *Proc. Soc. Exp. Biol. Med.* **46,** *565 (1941)*). Following Woolley's paper, Pavcek and Baum (*Science* **93,** *502 (1941)*) reported that inositol cured "spectacled eye" in rats reared on a purified diet. It is a common observation, however, that in many laboratories rats reared on purified diets apparently free of inositol do not develop any loss of hair around the eyes. Martin (*Am. J. Physiol.* **136,** *124 (1942)*) has presented evidence which indicates that an inositol deficiency may be precipitated by the inclusion of p-aminobenzoic acid in the diet. Animals receiving thiamin, riboflavin, pyridoxine, pantothenic acid, nicotinic acid, choline, inositol, and p-aminobenzoic acid as supplements to a purified diet developed normally. The removal of either inositol or p-aminobenzoic acid resulted in poor growth and changes in the fur coat, but when both were removed, the animals again grew normally. Martin suggests that the intestinal synthesis of inositol is prevented by the inclusion of p-aminobenzoic acid in the diet. However, Sure (*J. Nutrition* **26,** *275 (1943)*) has reported experiments which practically duplicate those of Martin, except that the levels of vitamins were different, and found no effect of either inositol or p-aminobenzoic acid on the growth of young rats. A report by Cunha, Kirkwood, Phillips, and Bohstedt (*Proc. Soc. Exp. Biol. Med.* **54,** *236 (1943)*) describes an alopecia, in rats reared on a natural diet composed chiefly of corn and soybean meal, which could be cured by inositol although only a few animals were studied.

The role of inositol in the nutrition of the lactating rat is similarly in dispute. Climenko and McChesney (*Proc. Soc. Exp. Biol. Med.* **51,** *157 (1942)*) found that on purified diets either with or without p-aminobenzoic acid the inclusion of inositol increased the milk yield of lactating rats, and the mortality rate of the young was much decreased. The inclusion of p-aminobenzoic acid alone appeared to have an adverse effect upon lactation. The reverse of this finding has been reported by Sure. The supplementation of the diet with p-aminobenzoic acid greatly improved lactation while inositol was decidedly injurious. Ershoff and McWilliams (*Proc. Soc. Exp. Biol. Med.* **54,** *227 (1943)*) observed that the addition of inositol to a purified diet containing sulfaguanidine resulted in reduced fertility in rats. Strangely enough, this disturbance did not occur if either sulfaguanidine or inositol was omitted from the diet.

These divergent findings cannot as yet be reconciled. It appears likely that differences in the intestinal flora may be concerned. The synthesis of certain factors by these organisms has been established (*Nutrition Reviews* **1,** *220, 341 (1943)*). The other possibility suggested by Martin, that under certain conditions a flora may be developed which is detrimental in the sense that it may crowd out a "vitamin synthesizing" flora or actually destroy certain vitamins, remains to be studied. Elvehjem (*Am. Scientist* **32,** *25 (1944)*) has pointed out that the level of other vitamins in the diet, such as riboflavin and pantothenic acid, may have an effect on the amount of various factors synthesized in the gastrointestinal tract. Thus, not only the qualitative but also the quantitative makeup of the diet may be of importance in determining the need for accessory food factors.

A lipotropic action for inositol was reported in 1941 by Gavin and McHenry (*J. Biol. Chem.* **139,** *485 (1941)*). These workers produced fatty livers in rats by feeding a beef liver fraction. Choline did not effect the fatty deposition, but both lipocaic and

inositol were effective in preventing its development. In 1942, Engel (*J. Nutrition* **24,** *175 (1942)*) found that weanling rats fed purified diets containing thiamin, riboflavin, pyridoxine, calcium pantothenate, and choline as water soluble vitamin supplements developed fatty livers. The addition of inositol decreased the fat deposition, especially when the choline supplement was low. Inositol thus appeared to have a sparing action on choline, and even at supposedly adequate levels of choline a detectable effect of inositol was found. Interest in these findings is renewed by the studies of Abels, Kupel, Pack, and Rhoads (*Proc. Soc. Exp. Biol. Med.* **54,** *157 (1943)*), which show that inositol apparently has a lipotropic effect on human subjects.

Abels and associates cite studies, as yet unpublished, made at the Memorial Hospital in New York in which it was found that the livers of patients with carcinoma of the gastrointestinal tract are almost always infiltrated with fat. Administration of 8 g. of lipocaic to 11 of these patients on the night before operation apparently caused a decrease in fatty infiltration because these 11 livers had only 46 per cent as much fat as did the control group. The question naturally arose as to whether the lipocaic itself exerted this effect, or whether it might be attributed to choline or inositol. Again, unpublished work is cited to indicate that the lipotropic activity was apparently not due to choline alone. This last finding is in agreement with the conclusions reached by Dragstedt (*J. Am. Med. Assn.* **114,** *29 (1940)*) in experiments with animals. Inositol remained to be tried.

When four times the amount of inositol present in the 8 g. doses of lipocaic were given to 8 patients with carcinoma of the gastrointestinal tract, the hepatic fat content of these patients was found at operation to be, with one exception, within normal limits. Another group of 10 similar patients was given 280 mg. of inositol during the last ten preoperative hours. This dose was equal to the amount of inositol contained in the previous doses of lipocaic. The hepatic fat content in this group of patients was only 50 per cent of that in the control group, and in only one patient was the fat significantly elevated.

These observations, therefore, not only confirm the conclusions of Gavin and McHenry and Engel that inositol possesses lipotropic properties, but also suggest that inositol may be responsible for the lipotropic effects of lipocaic.

NUTRITIVE VALUE OF BUTTERFAT, VEGETABLE OILS, AND OLEOMARGARINES

Studies of the comparative nutritive value of butterfat and of certain vegetable oils were reviewed several months ago (*Nutrition Reviews* **1,** *358 (1943)*). Experiments by Boutwell, Geyer, Elvehjem, and Hart (*J. Dairy Sci.* **26,** *429 (1943)*) were described which showed among other things that the type of carbohydrate in the diet influenced the growth response of young rats to various fats. For instance, when diets contained lactose as the sole carbohydrate, butterfat caused definitely better weight gains than did vegetable oils. However, when dextrose, sucrose, dextrin, or starch was substituted for lactose, the weight increases were at least as good with corn oil as with butterfat. These results suggested that butterfat is nutritionally superior to certain vegetable oils when lactose is the only or principal carbohydrate ingested, but not when other carbohydrates are included in the diet in large amounts. The same authors have now amplified their investigations to include seven commercially available oleomargarines, three of which were mixtures of animal fats and four, mixtures of hydrogenated vegetable oils (*J. Nutrition* **26,** *601 (1943)*). The current national and worldwide shortage of dairy products and the determined attempts of many people to

remove the taxes on oleomargarine give these studies economic as well as nutritional importance.

The experiments were done on groups of 21 day old male rats of the Sprague-Dawley strain. Carbohydrate in the ration was increased from the 32 per cent used in the first report to 48 per cent, because at this latter level the difference in growth rates between rats fed butterfat and those fed corn oil became more marked. The ration as used in the second study contained carbohydrate 48 per cent, fat 28 per cent, fat free casein 20 per cent, and salts 4 per cent. To every 100 g. of the dietary mixture, the following vitamins were added: 0.5 mg. of thiamin, 0.5 mg. of riboflavin, 0.625 mg. of niacin, 0.625 mg. of pyridoxine, 5 mg. of calcium pantothenate, 30 mg. of p-aminobenzoic acid, 100 mg. of inositol, 250 mg. of choline chloride, 0.014 mg. of calciferol, 0.560 mg. of beta carotene, 2.24 mg. of alpha tocopherol, and 0.21 mg. of 2-methyl-1,4-naphthoquinone. In each experiment, two parallel series of rats were used. One of the series received lactose as the only carbohydrate while the other was fed a carbohydrate mixture made up of lactose 3, sucrose 15, dextrose 5, starch 15, and dextrin 10 parts respectively. This mixture was modeled after the mixed carbohydrate diet such as man ordinarily consumes. The two series of animals were divided into groups each of which was fed one of the following fats: butterfat, lard, corn oil, coconut oil, cottonseed oil, soybean oil, olive oil, peanut oil, Crisco, or one of the seven commercial oleomargarines. Rations were made up weekly and stored under refrigeration between daily feeding periods. Weight gains were reported for five or six week periods. Ad libitum feeding was practiced.

It was again found that when lactose was the sole carbohydrate in the diet, vegetable oils were definitely inferior to butterfat and lard in promoting the growth of young rats. Under the same conditions, the animal oleomargarines were but slightly below butterfat in nutritive value, while all but one of the vegetable oleomargarines was distinctly inferior. With the mixture of carbohydrates substituted for lactose, however, equal growth was obtained from the animal fats and vegetable oils, and the gain was even greater for each group than it had been with lactose. Similar results were obtained with the oleomargarines (both animal and vegetable), several of which actually showed slight superiority to butterfat. In the experiments in which oleomargarines were used the figures for weight gain were checked by calculations of the per cent efficiency (grams gained divided by grams consumed and multiplied by 100) of the fats. The conclusion seems justified, therefore, that an interrelationship exists between the kind of carbohydrate and the kind of fat in the diet. The authors suggest that with the mixed carbohydrate diet, more carbohydrate is available for fat formation than with the lactose diet. Possible reasons for the better weight gain of lactose fed rats on butterfat than on vegetable oils have already been discussed (*Nutrition Reviews* **1,** *358 (1943)*).

Emphasis must be given to the fact that these conclusions are based on weight curves in rats for relatively short periods of time and are only tentatively drawn. Boutwell and associates intimate that they are also studying the growth of these animals to maturity and reproduction. The correctness of their deductions, therefore, will be tested further by additional observations. Great caution must be exercised in transferring these results to problems of human nutrition. If the deductions are right, however, they indicate that butterfat may be nutritionally superior to vegetable oils only during comparatively brief periods of human life: during infancy or at times when, for medical reasons, a patient may be placed on a predominantly milk diet. During the rest of life when foods containing different kinds of carbohydrate are ingested, vegetable oils may meet adequately the nutritional requirements for fat.

PROTEIN QUALITY OF PROCESSED CEREALS

Wartime shortages of animal protein have resulted in an appreciable increase in the consumption of protein from plant sources, with cereal grains playing an even more important role in supplying the protein necessary for an adequate diet. The relative nutritional efficiencies of the various cereal proteins have been at least qualitatively established by fairly extensive research during the past decade or so, and considerable data are at hand showing the effect of processing on the biologic value of many proteins, including certain of the cereals. Morgan (*J. Biol. Chem.* **90,** *771 (1931)*) observed that dry heat during processing impairs the growth-promoting value of wheat, rice, and corn proteins. Pronounced decreases in the palatability and nutritive value of the protein were particularly evident where the cereal (wheat, rice) was puffed by preheating with steam under high pressure, followed by suddenly releasing the pressure. Murlin, Nasset, and Marsh (*J. Nutrition* **16,** *249 (1938)*) found that heat processing of cereals lowers the biologic value of the protein for man, and confirmed the low rating for puffed wheat.

The paper by Murlin *et al.* showed the effect of varied processing conditions, as encountered in the many prepared wheat cereals, on the nutritive value of the marketed product. Similar results have been obtained with various oat cereal products. Stewart, Hensley, and Peters (*J. Nutrition* **26,** *519 (1943)*) studied the growth-promoting values of the protein of rolled oats, drum-dried oatmeal, an oven-expanded oat cereal, a gun-exploded cereal containing 75 per cent oat flour and 20 per cent corn and rye flours, and puffed oats. The authors placed 3 male and 3 female rats weighing 50 to 60 g. on each of the diets, and continued the test feeding for a fifty-six day period. In all cases the protein accounted for approximately 10 per cent of the ration.

In one series of three test diets, the feeding was ad libitum. In a second series of three diets, the intakes were restricted to that of the group on the ration which the animals tended to consume in the least amount. All animals in the final series of four diets were offered 7.0 g. of the test ration daily, most of which was consumed. All three series included one group of rats on a ration in which rolled oats furnished the protein, thus making it possible to compare the growth-promoting effects of the various cereals despite the slight changes in feeding procedure from one series to another.

In the first series, the oven-expanded oat cereal and drum-dried oatmeal proved equal to the rolled oats in protein quality, although the food intakes indicated that the rats had a definite preference for the rolled oats, since they consumed 20 per cent more food than the animals on the other test rations, and hence showed an appreciably greater weight gain during the period of the experiment. The second series demonstrated the high quality of the protein of "home" cooked oatmeal as against rolled oats, and showed a striking impairment in the biologic value of the gun-exploded oats-corn-rye cereal product. The rats on the latter diet gained only 17 g. during the fifty-six days, as against average gains of 46 and 43 g. for the other groups on the equalized restricted feeding test, in which the rolled oats ration consumed was only 60 per cent of that when feeding ad libitum.

That the severe heat treatment during processing is responsible for the low quality of the gun-exploded product is indicated from the performances of the rats in the third experimental series. Here an untreated mixture of oats, corn, and rye flours proved the equal of rolled oats, the former resulting in an average weight gain of 1.48 g. per gram of protein consumed as against 1.52 g. from rolled oats. The gun-exploded oats-corn-rye cereal, however, with an average growth-promoting value of 0.48 g. per gram of protein, was only one-third as efficient as rolled oats in supplying the

protein needs of the rat. Puffed oats, which had also been subjected to a high temperature and sudden expansion by pressure release, proved even more severely damaged, the gain of 0.34 g. per gram of protein consumed by the rats being less than one-fifth that obtained from the rolled oats ration. Again, the puffed cereals proved to be the least palatable, the rats consuming an average of less than 7.0 g. of the ration daily.

The data of Morgan, of Murlin and co-workers, and of Stewart and co-workers all indicate that the cereal proteins are severely damaged by heat processing. Explosion-expanded cereals such as puffed wheat, puffed rice, and puffed oats, are particularly altered with respect to protein quality. Murlin's data would indicate that the impairment is not one of lowering the digestibility, but rather is to be found in a lowered utilization of the protein, possibly as the result of destruction of certain of the essential amino acids. In rats, the impaired quality is made particularly evident because of the accompanying lowered palatability which results in a severely limited consumption of such materials.

The paper by Stewart *et al.* completes a gap in our knowledge of the effects of processing on the nutritive value of cereal proteins. The fact that oat protein has been considered one of the better cereal proteins, together with current trend in the American diet toward a greater consumption of cereals in ready-prepared—and hence processed-form, emphasize that the results of these experiments are of definite interest and concern not only to nutritionists but also to the food processors.

CITRIN DEFICIENCY IN GUINEA PIGS

The evidence for "vitamin P" deficiency in guinea pigs and rats and its cure by "citrin" preparations has been reviewed recently (*Nutrition Reviews* **1,** *214 (1943)*). At that time doubt was expressed concerning the reliability of the capillary fragility test as an index of the supposed deficiency. The biologic test of Bacharach, Coates, and Middleton (*Biochem. J.* **36,** *407 (1942)*) in which the "critical petechial pressure" was measured, has aroused some comment because of the extraneous factors which may affect the measurement, and the necessity for statistical analysis in the interpretation of the results. Although the drop in capillary resistance reported by Bacharach and co-workers was small, it was considered significant by the authors.

Bourne (*Nature* **152,** *659 (1943)*) feels that his recent results no longer leave any doubt that a marked drop in capillary resistance can be obtained in guinea pigs, a decrease which can be specifically reversed with "citrin." Instead of employing the first appearance of petechial hemorrhage as an end point to determine the capillary resistance, Bourne utilizes a somewhat different criterion. A 20 mm. suction-cup was placed on the shaved, vaselined skin. The pressure was rapidly lowered to a given level and released after ten seconds. The measure of capillary resistance was taken as the negative pressure at which sufficient petechiae developed that a uniform reddish purple color or hematoma occurred. If with a given animal the chosen pressure level failed to produce the hematoma, another section of skin was tested with a lower pressure until the desired effect was obtained.

A group of 54 guinea pigs was placed on a typical scorbutogenic diet. Each animal was given 10 mg. of ascorbic acid daily by mouth. At the start of the experiment, 30 of the animals did not develop a hematoma at 560 mm. mercury or more, and the remaining 24 animals developed a hematoma at 460 to 560 mm. pressure. After three to eight weeks on the diet, all the animals

showed at least a 50 per cent decrease in capillary resistance, and in many cases an even greater decrease occurred. In 15 of the animals, a daily intake of 10 mg. of "citrin" produced a rise in capillary resistance of 60 to 100 per cent within seven days. In the control animals the capillary resistance remained low, although in a few instances a spontaneous rise in resistance, never more than 20 per cent, occurred. When "citrin" was discontinued, the capillary resistance was again reversed, but during this phase a fatal bronchopneumonia sometimes occurred. The results were considered sufficiently clearcut that statistical treatment of the data was unnecessary, although as a matter of interest the author applied statistical methods to his data.

The author gives no description of the "citrin" preparation. The value of Bourne's contribution lies in its apparent clearer demonstration of the fall in capillary resistance on the deficient diet and its reversal upon treatment.

MEASURING THE BIOLOGIC VALUE OF PROTEINS

Definite experimental conditions and concepts are necessary for the ideal solution of the problem of biologic evaluation of proteins. This viewpoint is presented in a paper by Mitchell of the University of Illinois (*J. Animal Sci.* **2,** *263 (1943)*). The author is emphatic in pointing out that precise conditions must obtain if proteins are to be evaluated accurately. Nevertheless, it is recognized that the ideal conditions are impossible to realize with some species or are so difficult or costly to attain that they are prohibitive. In other instances, it is pointed out that certain departures from the ideals set up are permissible within limits. Such departures, however, do not conflict with certain basic considerations of the digestion and metabolism of proteins.

The author points out the relative importance of fecal nitrogen of body origin, the so-called metabolic nitrogen, in any determination of protein digestibility. This fraction of the fecal nitrogen in animals such as the rat, dog, pig, and man averages about 0.20 to 0.25 g. per 100 g. of dry matter consumed. The true digestibility of protein is thus considerably higher than the apparent digestibility, and the difference between these two values becomes greater the lower the protein content of the feed.

Dietary nitrogen serves two purposes in the animal body: (1) the maintenance of the nitrogenous integrity of the tissues, and (2) the productive function of furnishing the structural material in the formation of new tissues or secretions. Both must be considered in evaluating dietary protein. To consider the productive function of protein, as for growth, to the exclusion of the maintenance function, leads to an underestimation of the former which increases in magnitude as the rate of production decreases. Since the amino acid requirements for maintenance are probably simpler than those for the construction of new protein, it may be expected that the utilization of dietary nitrogen in metabolism will be greater for maintenance than for production. Presumably the utilization of dietary nitrogen for maintenance must be satisfied before production can occur. After the withdrawal of amino acids from blood for maintenance purposes, there is left, for protein synthesis, a different assortment of amino acids from that contained in the original protein supply. In a growing organism, however, it is evident that both types of metabolism occur simultaneously, rather than in strict sequence.

The percentage utilization of absorbed nitrogen may be expected to drop abruptly beyond the level that completely satisfies the nitrogen requirements. Hence the biologic evaluation of protein must be made at levels of protein intake that are just adequate to

satisfy the nitrogen requirements or that are definitely inadequate. Such levels will be different for each source of dietary protein.

With respect to the nutritive value of proteins for maintenance and growth, a unit of body gain does not possess a constant and definite significance owing to the varying composition of the body gains, nor do differences in rates of gain on the same level of protein feeding, with different sources of protein, accurately reflect differences in the nutritive value of the various protein mixtures under test. Mitchell is emphatic in pointing out that these inaccuracies may be increased by ad libitum feeding.

The biologic values of different proteins are not necessarily additive. They may be additive for mixtures of proteins having different amino acid deficiencies, but if two or more proteins or protein mixtures happen to have the same limiting amino acid they will not supplement one another when combined.

The biologic value of the nitrogen of feeds in the case of ruminants, especially, involves a consideration of the synthesis of proteins from simple forms of nitrogen by microorganisms in the digestive tract. Thus ruminants are able to utilize the nitrogen of feeds differently than nonruminants and probably better for those feeds containing a large proportion of their nitrogen in nonprotein form.

The theory of protein metabolism upon which the calculation of the biologic value of proteins rests is based upon an assumption of the validity of a distinction, first made by Folin, between a constant catabolism of nitrogen, related to body size and other body factors, and a variable catabolism of nitrogen dependent upon the level of protein consumed. Schoenheimer, Ratner, and Rittenberg (*J. Biol. Chem.* **130,** *703 (1939)*) have demonstrated a state of dynamic, not static, equilibrium between tissue proteins and the amino acids of the blood plasma and intercellular fluids which, in Mitchell's opinion, is not out of harmony with the original concepts involved.

The features essential to the ideal solution of the biologic determination of protein values of feeds and rations are also enumerated by Mitchell. It is held that the measurement selected should be absolute, not relative, measuring without reference to any other value, the utilization of the protein in the animal body, both in digestion and metabolism. It should be based on the unique function of protein to provide the body with nitrogenous compounds for its upkeep and for its productive functioning. The proteins and protein mixtures should be incorporated into rations otherwise nutritively complete and should provide all of the dietary nitrogen. Definite levels of feeding must be selected for each type of experiment. The ideal level for measuring the biologic value of dietary nitrogen for maintenance would seem to be that which just supports nitrogen equilibrium in adults.

For measuring the biologic value of dietary nitrogen in promoting growth and other productive functions, the ideal level seems to be that which just promotes maximum nitrogen retention. This will vary with the age and size of the animals. Account must be taken of the losses of dietary nitrogen to the body both in digestion and metabolism involving also the estimation of food and body nitrogen in feces and urine. The metabolic fecal nitrogen may be best estimated by measuring the fecal nitrogen per unit of dry matter consumed when the ration contains no nitrogen. Endogenous nitrogen may be estimated by measuring the urinary nitrogen per unit of body size (surface area) on a nitrogen free ration. These measurements can be made in the same "standardizing" period preceded by a period in which an approximately constant output of nitrogen in the feces and urine is obtained. Obviously, prolonged periods are inadvisable, especially with protein of low biologic value.

Having thus estimated that portion of the fecal nitrogen which is of body origin, the coefficient of true digestibility of the food nitrogen may be obtained. The metabolic efficiency of utilization of digested nitrogen

is measured by the proportion of the truly absorbed dietary nitrogen that is not excreted in the urine. This is the "biologic value," a measure which credits the absorbed nitrogen with all of the synthetic processes of the body that it promotes, while it distinguishes between such processes and other syntheses such as that of fat. Body gains, as indices of protein utilization, do not make this distinction since they consist of both protein and fat.

Biologic values of protein may be obtained with rats, with some other small laboratory animals, and with swine, without any compromise of the ideal conditions set up for nitrogen metabolism experiments. The nitrogen balance itself can also be determined in a properly executed carcass analysis study, although an experiment of much longer duration is required. A nitrogen free diet is not absolutely requisite to the ideal experiment. A ration containing a small proportion of protein that is almost completely utilized in digestion and metabolism may be employed in both the standardizing period and test period. It is also possible to estimate the metabolic nitrogen in the feces and the output of endogenous nitrogen in the urine per unit of body surface, once they have been determined for a given species and found to be sufficiently constant. While it is enlightening to distinguish between the utilization of nitrogen in digestion and metabolism, data for maintenance and production also serve a proper usefulness, especially if the animals concerned are of the same size and may be presumed to have the same maintenance requirement of protein. Comparative or relative results such as may be obtained by using a specific protein as a standard are not in the same category as absolute protein values, but may serve a proper usefulness.

The author states that so-called practical methods of evaluating proteins biologically may yield misleading information. Body weight gain, especially when the food intake is not controlled, possesses such variable chemical composition that its significance as a measure of protein utilization is dubious. Gain in body weight, dimension, or in body nitrogen, or in the production of milk or eggs does not involve or measure the use of dietary nitrogen in maintaining the body's store of nitrogen. Ad libitum feeding cannot be used in an experiment in which relative biologic qualities of proteins are being compared. Palatability, regardless of protein quality, becomes a factor in ad libitum feeding and may grossly exaggerate the difference in nutritive value between two protein mixtures. Further, it is in error to relate food protein intake to body gains as a measure of protein efficiency, since the ratio of dietary protein consumed to gain in body weight secured is closely correlated with the rate of gain itself.

Mitchell is emphatic with regard to experiments in which food intakes are not controlled. Ad libitum feeding, he contends, has its proper place only in the purely practical experiment in which neither the meaning of the results obtained nor their relation to a particular nutrient consumed is considered to be of vital importance.

B-VITAMINS AND THE TOXICITY OF PROMIN

Promin (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) is a chemotherapeutic agent which has excited considerable experimental interest because it exerts a favorable effect on the course of experimentally induced tuberculosis in guinea pigs (Feldman, Hinshaw, and Moses, *Am. Rev. Tuberc.* **45,** *303 (1942)*; Feldman, Mann, and Hinshaw, *Am. Rev. Tuberc.* **46,** *187 (1942)*). Practical therapeutic use of promin, however, is prevented because the substance has so many severe toxic reactions (Higgins, *Am. J. Clin. Path.* **13,** *28 (1943)*). The toxic effects include hyperirritability,

paralysis of the hind limbs, anorexia, cyanosis, and a hemolytic type of anemia. Higgins (*Am. J. Med. Sci.* **207,** *239 (1944)*), in attempting to find something which would alleviate these toxic manifestations, has discovered that excessive intake of thiamin, riboflavin, and pyridoxine protects white rats against the toxicity of promin.

Rats were used for the experiment because they react to promin in ways similar to those of the guinea pig and are more suitable for dietary studies. Male animals weighing 70 to 85 g. were fed a purified diet made up as follows: sucrose, 76 parts; vitamin-free casein, 18 parts; corn oil, 2 parts; salt mixture, 4 parts. Supplements of cod liver oil were given. The rats were placed in a circular maze cage in which light amber bottles of liquid were available to them: two of distilled water and one each of thiamin, riboflavin, pyridoxine, calcium pantothenate, niacin, and choline chloride. The aqueous solutions of the vitamins were attached at places inconvenient for the rat to reach, and the positions of the bottles were changed frequently. The concentrations were arranged so that each ml. of the aqueous solutions contained, respectively, 100 micrograms of thiamin, 200 micrograms of riboflavin, 100 micrograms of pyridoxine, 200 micrograms of calcium pantothenate, 1 mg. of niacin, and 10 mg. of choline chloride. Record was kept daily of the food and vitamin intake. After one week in the cage, 50 mg. of promin were given each day for three weeks. Two types of control animals were used: one was given promin without access to the B-vitamins and the other was given the vitamins without promin. Another group of 10 animals was subjected to the same experimental conditions, but instead of receiving the vitamins ad libitum, each rat was fed by tube daily 1 ml. of a solution containing 100 micrograms of thiamin, 200 micrograms of riboflavin, 100 micrograms of pyridoxine, 200 micrograms of calcium pantothenate, 1 mg. of niacin, and 10 mg. of choline chloride. At the end of the three weeks of promin administration, all animals were exsanguinated under light ether anesthesia.

Controls given the fractions of vitamin B by tube, but no promin, developed normally. Those fed in a similar manner but given 50 mg. of promin per day become irritable within twenty-four hours. They became excited and a number chewed their own tails and paws. In a few days, alopecia developed, cyanosis appeared, and the food intake was reduced by about half. With continued administration of the drug, tolerance for it seemed to develop; food intake gradually increased and the nervousness subsided, but the alopecia was not relieved. The animals which received the drug but allowed free access to the B-vitamins remained indistinguishable in general appearance from the controls not given promin, although they did not gain as much weight. Spontaneously, however, they increased their intake of thiamin, riboflavin, and pyridoxine often as much as six times. Their intake of niacin and choline chloride remained unchanged; during the third week of promin administration, slightly greater quantities of calcium pantothenate were consumed. The rats given the restricted amounts of the vitamin + promin developed the following hematologic changes: marked crenation of erythrocytes, a macrocytic anemia of 3,250,000 to 4,800,000 cells per cu.mm., and a reticulocytosis of from 47 to 72 per cent. In contrast, animals which received the drug but were allowed free access to the B-vitamins showed minimal crenation, less macrocytosis, less severe degrees of anemia (red cell count averaged 2 million cells higher), and less than half as many reticulocytes. Hemoglobin levels in the two groups were not statistically dissimilar.

It is interesting that the intraperitoneal injection of like amounts of promin had but slight effect on the weight and general appearance of the animals. For this reason, Higgins suggests that some of the toxic changes induced by the drug "bear some

relation to chemical changes which occurred in the gastrointestinal tract."

These results, therefore, demonstrate that increased dietary intakes of thiamin, riboflavin, and pyridoxine counteract the toxic effects of orally administered promin. That the animals selectively chose to increase their consumption of these three vitamins is in itself not without interest. The mechanism by which the protection is effected is not clear and one wonders whether the chemotherapeutic value of promin is altered when large amounts of thiamin, riboflavin, and pyridoxine are allowed. If not, it is not inconceivable that the toxic manifestations may eventually be controlled enough to permit more exacting evaluation of the influence of promin on tuberculous infections. The author avoids discussion of this last possibility. Any practical therapeutic value of these results may be lessened, however, because two related sulfones, diasone and promizole, which also have some chemotherapeutic influence on experimental tuberculosis, are considerably less toxic than promin (Feldman, Hinshaw, and Mann, *Proc. Staff Meetings Mayo Clinic* **19,** *25 (1944)*). The ability of the B-vitamins to counteract any toxic manifestations of these two drugs should also be evaluated.

SUDDEN DEATH IN ASSOCIATION WITH FATTY LIVER

Investigators in the field of experimental nutritional deficiencies are familiar with the association of fatty livers and sudden death in experimental animals. Goldberger, Wheeler, Lillie, and Rogers (*Pub. Health Reports* **43,** *1385 (1928)*) described fatty livers in dogs which had been placed on a blacktongue producing diet. Sebrell (*Ibid.* **44,** *2697 (1929)*) reported the occurrence of sudden death in these animals and later (Sebrell, Onstott, and Hunt, *Ibid.* **52,** *427, (1937)*) described a symptom-complex in dogs which was characterized by sudden collapse and coma promptly followed by death unless treated early with adequate doses of riboflavin. The livers in these animals were yellow and fatty.

Fatty livers have also been produced experimentally in other ways. The studies of Best and Huntsman (*J. Physiol.* **75,** *405 (1932)*) in which the action of choline in preventing the accumulation of liver fat was described, are now well known, as is the literature which followed their reports.

In the light of these experimental observations, the report of 11 cases of sudden death occurring in relatively young adults by Graham (*Bull. Johns Hopkins Hosp.* **74,** *16 (1944)*) is especially interesting. In all of the cases the striking pathologic finding was an extremely fatty liver. In 6 of these there was an additional lesion present at autopsy which could have been regarded as the cause or the main contributing cause of death. But in 5 cases there was no lesion to explain the death of the subjects other than a diffusely fatty liver. These 5 cases are described in detail. Their ages ranged from 27 to 40 years, all were white, and their economic and social status were somewhat above average. Their past history was singularly negative except for a history of alcoholism. This was definitely present in 3 of the 5 cases and was probably present in another. In 5 of the 6 cases which are not presented in detail, a definite history of alcoholism was also obtained.

Three of the 5 individuals had attacks of unconsciousness prior to death and in one of these the attacks were described as epileptic or convulsive. One had experienced vague symptoms of weakness and anorexia for several months prior to death. In 3 of the cases death occurred within a half hour or less from the time of collapse. In one, death occurred during sleep and in the fifth there was a period of several hours of coma preceding death. It is noteworthy that one of

the subjects had been under the observation of a group of physicians (an induction board) for almost the entire day of his death without being considered acutely or seriously ill. Another was discharged from the hospital the same day that death occurred.

The pathologic changes in the liver were striking. In 3 of the cases no normal liver cells could be found. Each liver cell was variably distended with a fat globule and in some the globules of fat were so large as to compress the nuclei into a crescent shape. In the other 2 cases the picture was only slightly less marked.

These cases are of interest because it is not improbable that death may have occurred as a result of nutritional deficiency and thus they may be comparable with the nutritional deficiencies accompanied by fatty livers which have been described experimentally. Dietary histories are not given in the report, but it is suggested that since most of the subjects had indulged excessively in alcohol, their diets may well have been poor for a long time.

There are other possible explanations for these instances of sudden death and of these hypoglycemia must be given first attention. Marked fatty infiltration of the liver has been observed in cases of spontaneous hypoglycemia (Judd, Kepler, and Rynearson, *Am. J. Surgery* **24,** *345 (1934)*). It is not unlikely that hypoglycemia may have been the actual cause of death in Graham's cases for livers such as he describes could scarcely have stored glycogen. However, a nutritional deficiency might well have been the underlying cause of the fatty liver.

GALACTOPOIETIC EFFECT OF THYROXINE

Graham in 1934 (*J. Nutrition* **7,** *407 (1934)*) observed that orally administered dried thyroid gland as well as subcutaneously injected thyroxine caused a temporary stimulation of milk production in dairy cows. Since that time there has been some speculation on the possible usefulness of this reaction of the mammary gland to thyroid and thyroxine as a practical means to increase milk production in dairy herds. Until 1939, however, thyroid and thyroxine were comparatively expensive products. The situation was changed in that year when Ludwig and von Mutzenbecher (*Z. physiol. Chem.* **258,** *195 (1939)*) reported the isolation of thyroxine from hydrolysates of casein treated with iodine (iodinated casein) and thus made it possible to obtain thyroid-active material at low cost.

The new procedure has been exploited by Blaxter (*Nature* **152,** *751 (1943)*), who reports results of large-scale experiments on the milk production of dairy cows fed iodinated proteins. The experiments were carried out under the auspices of the British Agricultural Research Council and involved 208 dairy cows. Both plant and animal protein were used. "Ardein," a commercial preparation of the ground nut (Arachis hypogoea) rich in the globulin arachine, was iodinated under semicommercial conditions and the iodinated "Ardein," containing 0.88 per cent acid insoluble ("thyroxine") iodine, was used. When 50 g. of this material was fed per day (*i.e.*, 0.4 to 0.5 g. iodine), milk production increased 35 per cent and fat production 54 per cent. At the same time the resting pulse increased 30 per cent and the resting respiration rate, 34 per cent. If no extra food was given to compensate for the increased metabolism, the cows lost almost 10 per cent of their original body weight after seven weeks' feeding of the iodinated proteins. When treatment was stopped live weight was rapidly regained, and there was no indication that the health of the cows had been impaired by the drastic treatment.

Iodinated casein had the same effect as iodinated "Ardein." It was found that a dose of 15 g. daily of iodinated casein in-

creased milk production by approximately 16 per cent and a 30 g. daily dose by 33 per cent, indicating that the percentage response in milk production is directly proportional to dosage within this range. The heart rate increase, however, is nearly trebled by doubling the dosage.

The galactopoietic potencies of iodinated proteins, expressed in terms of the percentage increase in milk production per gram of iodinated protein fed, were the following: 0.075 for iodinated blood, 0.543 for iodinated "Ardein," and up to 1.096 for iodinated casein. There was a distinct relationship between the acid insoluble ("thyroxine") iodine analysis of iodinated proteins and their galactopoietic potencies.

It was found that the response in milk production to a standard dose of a thyroid-active preparation is dependent on the initial level of production of the cow. The absolute response (in pounds per day) is greater the higher the initial yield, but the percentage response declines with increasing initial yield.

The stage of lactation of the cow is the main factor causing variations in the initial yield. Blaxter believes that during early lactation a larger amount of mammary tissue is in a higher state of activity, whereas late in the lactation, the gland has a lower activity per unit tissue.

It has been found that feeding iodinated proteins does not prolong milk production in cows approaching the end of their normal lactation period. Experiments are in progress to find whether practical application of the results is possible, especially with regard to winter milk production.

ASCORBIC ACID: NITROGEN RELATIONSHIPS IN GRAPEFRUIT

Although the field of nutrition is ordinarily restricted to the nutrition of man and animals, studies of the nutrition of plants have proved of tremendous practical value and are of great concern to students of human nutrition. In the last analysis, we depend directly or indirectly upon plants for all of our food, with the exception of a few minerals and, of late, of some of the vitamins. Not only are we concerned with nourishing plants so as to bring optimal growth and hence optimal profit to the producer, but we are as much or more interested in obtaining vegetable foodstuffs of optimal food value to the consumer. The latter objective may be attained by an investigative program in which each plant foodstuff is first examined to establish its chief contribution to the diet, following which the growth conditions are determined which in each case will yield a plant product containing maximal quantities of these dietary components.

Citrus fruit are nearly unique in that they make but one major contribution to the diet, namely, ascorbic acid (vitamin C). The objective of the consumer-minded producer, therefore, is to raise citrus fruit of maximal ascorbic acid content, without of course sacrificing palatability.

An investigation has been started at the Agricultural Experiment Station of the University of Arizona to determine the relation of soil conditions to the ascorbic acid content of grapefruit from trees grown in these soils. Martin (*Univ. Ariz. Tech. Bull.* **97** (*1942*)) had previously noted that trees which had a diminishing supply of nitrogen during the period of fruit growth yielded grapefruit that were sweeter, thinner skinned, better colored and shaped, and in general of better market grade than fruit from trees which were maintained on a high nitrogen nutrition. Jones and associates (*Science* **99**, *103* (*1944*)) have now added that juice from the grapefruit of trees with a low nitrogen supply contains 20 per cent more ascorbic acid than that from the fruit of trees with high nitrogen nutrition. The

investigators analyzed more than 500 Marsh grapefruit from 8 trees. The juice from the 4 trees on a low nitrogen plot averaged 46 mg. per cent ascorbic acid as compared to 38 mg. per cent from the trees on a high nitrogen plot.

Of possibly even greater interest are comparisons that were made between the vitamin C and nitrogen content of the juice from 15 trees raised under special experimental conditions. (The conditions are not given in the article.) A well defined negative correlation between nitrogen and ascorbic acid was observed (negative correlation coefficient = 0.91). The lowest ascorbic acid concentrations, about 40 mg. per cent, were correlated with nitrogen values of 100 mg. per cent, whereas at the highest ascorbic acid concentrations, 70 mg. per cent, the juice contained only 45 mg. per cent nitrogen. These high ascorbic acid values are unusual for grapefruit juice.

The authors speculate as to the possible explanation for this inverse relationship. They suggest that perhaps the high nitrogen concentrations are correlated with high ascorbic acid oxidase values, which enzyme might be expected to destroy part of the ascorbic acid. It would not be difficult to determine whether such a correlation actually exists.

The authors point out the value of similar studies on other fruits and vegetables, and on grapefruit from other regions. It seems certain that great profit may accrue to the health of the nation if the "consumer's viewpoint" is continued as a basis for further studies of plant nutrition.

REGULATION AND SIGNIFICANCE OF PLASMA VITAMIN A LEVEL

Of the various procedures for the measurement of vitamins, there are only a few which have been so simplified that they can be carried out in any clinical laboratory. One of the latter is the measurement of plasma vitamin A. This has now been measured in a variety of clinical conditions and it is timely to consider some of the circumstances under which the plasma vitamin A level is altered from the normal.

Using the procedure based on the Carr-Price reaction, Popper and Steigmann (*J. Am. Med. Assn.* **123,** *1108 (1943)*) summarize their observations in 2673 determinations on 454 patients. They also give normal values based on standardization of the color reaction against crystalline vitamin A and standard oils. In males the average vitamin A value was 58 micrograms per 100 ml. of plasma and the carotenoids 74 micrograms, with a vitamin A to carotene ratio of 0.78. In women the average vitamin A was 47 micrograms, the carotenoids 85 micrograms, and the ratio 0.57. The authors made no correction of their vitamin A value for the color developed by the carotenoids, since the color which carotene develops with antimony trichloride was found negligible under the conditions of the test employed.

Determinations made at intervals during twenty-four hours showed no significant variations in plasma vitamin A, nor were there significant changes over an eighteen day period. Variations of the carotenoid levels, in comparison, were pronounced.

In uncomplicated gallbladder disease, plasma vitamin A and carotenoid levels were within the normal range. In incomplete extrahepatic biliary obstruction without evidence of liver damage, the average plasma vitamin A level was somewhat but not significantly lower than normal. However, when there was evidence of secondary hepatitis and impairment of the liver function, the plasma vitamin A level was considerably reduced and in a great number of cases zero levels were found. This was also true when there was complete biliary obstruction if hepatic disease existed.

In cases of cirrhosis of the liver without

jaundice a moderate decrease in the plasma vitamin A level was found. The level tended to be lower in patients in the more advanced stages. It is interesting that in patients with hepatitis the plasma vitamin A level tended to rise above normal as recovery occurred.

A reduction in plasma vitamin A was also observed in a variety of conditions such as carcinoma of the stomach, pernicious anemia, and various infections. No significant alterations were found in peptic ulcer, diabetes mellitus, or in hyperthyroidism. High plasma vitamin A levels were observed in patients with renal disease.

In speculating as to the cause of the low plasma vitamin A level in liver disease, the authors call attention to the sharp drop which may occur in the course of a few days in cases of acute hepatitis. A similar change is observed in pneumonia. This makes it seem unlikely that impairment of intestinal absorption of vitamin A is the cause of the low plasma value for it is known that the plasma level falls extremely gradually when the diet contains no vitamin A whatever. It has been shown that in acute liver damage, the liver is not always depleted of vitamin A but in fact may show considerable vitamin A stores. Therefore, one can hardly attribute the low plasma vitamin A level to a failure on the part of the liver to convert carotene to vitamin A. According to the observations of Popper, Steigmann, Meyer, and Zevin (*Arch. Int. Med.* **72,** *439 (1943)*) with the fluorescence microscope, the distribution of vitamin A in the liver is found to be changed materially in the presence of liver disease. The vitamin A fluorescence shifts from its normal sites (fine lipid droplets on the edge of the liver cells and the Kupffer cells) to pathologic areas in the liver. The authors suggest that from such areas vitamin A may be less readily discharged and therefore is less available for utilization.

A further indication of the relationship of the liver to the plasma vitamin A level is found in the study by Lewis, Bodansky, and Shapiro (*Am. J. Dis. Child.* **66,** *503 (1943)*). These workers became interested in the sharp drop in the concentration of vitamin A in the blood which occurs during the first forty-eight hours of life and the sudden rise to normal on the fourth day. In previous experiments on rats Lewis, Bodansky, Falk, and McGuire (*J. Nutrition* **23,** *351 (1942)*) found that the concentration of vitamin A in the blood dropped to low levels only when the livers were devoid or almost devoid of vitamin A. From this it was concluded that the concentration of vitamin A in the blood gave some indication of the degree of vitamin A storage in the body. Examinations of the livers of 24 newborn infants, however, showed these to contain considerable quantities of the vitamin. It was necessary, therefore, to find some other explanation for the temporary drop in the plasma vitamin A shortly after birth.

A number of newborn infants were given a diet devoid of vitamin A and the plasma content of the vitamin was followed closely. It was found that in spite of the deficient diet, a spontaneous rise in the vitamin A concentration in the blood occurred. This suggests that the observed fall is more likely due to a failure in the mechanism of release of vitamin A from the liver than to lack of the vitamin in the diet. The authors suspected nevertheless that other factors might be involved in producing the fall in the plasma vitamin A level. In order to determine to what extent the usual low intake of vitamin A in early life affects the fall, plasma levels were followed in 8 infants receiving the vitamin. In half of the infants the supplement failed to maintain the blood level at a higher value than in infants receiving no such supplement. Analysis of the meconium showed little vitamin A, suggesting that there was no failure of absorption.

These observations suggest that in addition to the factors which have been recognized hitherto as influencing the plasma

vitamin A level, mobilization of the vitamin from the liver must be considered as well. In the newborn infant absorption seems good and storage in the liver is high, but for a few days the vitamin is not mobilized for passage into the plasma as readily as occurs later. Again, according to the studies cited, failure of mobilization may occur in the presence of liver disease. Perhaps the same explanation holds for the low levels observed during infections such as pneumonia. These studies uncover another mechanism whereby tissue supplies of a nutrient may be altered by means other than a faulty diet.

NUTRITIONAL DEFICIENCY AND SUSCEPTIBILITY TO POLIOMYELITIS

The relationship of vitamin deficiency to susceptibility to infections has been a subject of interest for some time, but a consistent picture has not been evident (*Nutrition Reviews* **1,** *298* (*1943*)). It is often assumed that the healthy, well nourished individual or animal is more resistant to disease than one that is nutritionally deficient. Actually this has not always been found to be so. Thus, for example, susceptibility to sarcoma virus in chickens and to spontaneous and induced tumors in mice has been found lower in unhealthy animals or in those given deficient diets (Rous, *J. Exp. Med.* **13,** *397* (*1911*); Tannenbaum, *Am. J. Cancer* **38,** *335* (*1940*)). Again, unhealthy or malnourished rabbits have been found to show less reaction to vaccinia virus than perfectly healthy animals (Rivers, *Infantile Paralysis, Symposium, p. 57* (*1941*)) and those on a starvation diet have been found to be more resistant to the virus than regularly fed animals (Sprunt, *J. Exp. Med.* **75,** *297* (*1942*)).

With reference to poliomyelitis, the evidence has been contradictory. McCormick (*Med. Record* **150,** *303* (*1939*)) considered the diets of victims of infantile paralysis to be frequently low in vitamin B_1 and claimed good results in paralytic cases by administering large amounts of thiamin. The excretion of thiochrome in the urine of 7 patients, however, was found by Ward, Sabin, Najjar, and Holt (*J. Bact.* **45,** *86* (*1943*)) to be within normal limits. Jungeblut's claim (*J. Exp. Med.* **66,** *459* (*1937*)) that the incidence of paralysis in monkeys could be reduced by the administration of large amounts of crystalline vitamin C, could not be confirmed by Sabin (*J. Exp. Med.* **69,** *507* (*1939*)). Toomey's observations in monkeys (*Am. J. Dis. Child.* **53,** *1202* (*1937*)) revealed no protection against the intracerebral inoculation of poliomyelitis virus on the part of vitamins A, C, or the B-complex, but there seemed to be almost complete protection offered by vitamin D. Sabin, Ward, Rapoport, and Guest (*Proc. Soc. Exp. Biol. Med.* **48,** *451* (*1941*)) could not confirm these observations.

Foster, Jones, Henle, and Dorfman bring further evidence bearing on this subject (*J. Exp. Med.* **79,** *221* (*1944*)). Mice were used as experimental animals rather than a smaller number of large animals in an attempt to obtain results with more statistical significance. The Lansing strain of mouse-adapted virus developed by Armstrong was used and the experiments seemed to have been well controlled.

In their first series three groups of animals were used. The diet fed was the same except for the content of thiamin. The mice were inoculated twenty days after being placed on the experimental diet and in one group the inoculum consisted of normal brain instead of poliomyelitis virus. The results showed little difference in mortality but there was a marked difference in the incidence of paralysis between the high thiamin and the low thiamin group inoculated with the standard dose of virus. Of 79 mice given 100 micrograms of thiamin per 100 g. of diet and inoculated with virus, 75 per cent developed

paralysis by the twenty-first day. In contrast to this, of 77 mice which were given only 10 micrograms of thiamin, only 9 per cent showed paralysis over the same period.

Further experiments were carried out in which an attempt was made to keep the vitamin deficient animals alive and at approximately constant weight by varying the amount of thiamin in the diet. The animals received 10 to 50 micrograms of thiamin. The results were similar to those cited above. Deaths in the group of animals receiving the low thiamin diet were substantially lower than among those receiving the high thiamin diet; in the low vitamin group the deaths among animals receiving injections of normal brain were nearly as great as among those receiving injections of virus. This finding suggested that the deaths in the low thiamin group were attributable for the most part to the vitamin deficiency itself. In one series of 55 animals receiving 100 micrograms of thiamin per 100 g. of diet, 85 per cent were dead in twelve days and 96 per cent in forty-six days. On the other hand, of 166 animals receiving the same dose of virus but only 10 to 35 micrograms of thiamin, only 20 per cent were dead in twelve days and 69 per cent in forty-six days. The control group inoculated with normal brain and receiving the low amounts of thiamin showed 11 per cent of deaths at twelve days and 19 per cent at forty-six days. Paralysis in the high thiamin group was 75 per cent at twelve days and 82 per cent at forty-six days, whereas in the low thiamin group there was only 12 and 41 per cent at these periods, respectively.

In order to determine whether restricted food intake in the thiamin deficient mice could be the cause of these striking differences, controlled experiments were carried out to study the effects of a total restriction in diet as well as of a restriction in which only carbohydrate was reduced. The results suggested that restriction of food was associated with an increase in the resistance of the animals to the virus. This resistance was shown in the incidence of both death and paralysis. Restriction of calories had approximately the same effect as restriction of the complete diet. Further observations suggested that these effects occurred without relation to the intake of fluid, a variable which was considered as possibly influencing the results since animals which are deprived of sufficient food occasionally voluntarily restrict their water intake.

A further study was made to determine whether restriction of diet or thiamin lack was the major factor in the production of increased resistance to poliomyelitis virus. This revealed that restriction was associated with delay in the action of the virus even though the amount of thiamin given such animals was greater than that given a group of mice whose diets were not restricted. Thiamin lack, on the other hand, appeared actually to prevent paralysis in many cases.

These observations, surprising though they may seem to be, are in line with studies by other workers. Rasmussen, Waisman, Elvehjem, and Clark (*J. Bact.* **45,** *85 (1943)*) reported similar observations in mice and Pinkerton (*Bact. Rev.* **6,** *37 (1942)*) found similar results in riboflavin deficient animals.

The observations are important because they imply so much regarding the relationship of nutritional deficiency to virus infections. Is it possible that a reduction in the food intake of an animal so reduces the nutrients available within cells that growth and development of virus units are compromised? Is it possible that aside from the availability of nutrients, interference with the vital or life processes of a host cell is something to which a virus is susceptible?

Another possible explanation of the observed increased resistance of deficient animals is that restriction of food in some manner interferes with the spread of a virus. Another factor to be considered which the authors of this interesting study did not explore, is the effect on the spread of an infecting virus due to the altered physical activity usually associated with nutritional deficiency and restricted food intake.

DEVELOPMENT OF LIVER INJURY IN RATS ON YEAST PROTEIN DIET

A new method of food production, which is supposed to be more economical and adaptable than conventional agricultural methods, is being developed, based upon certain strains of yeast that will grow rapidly when mixed in large tanks with molasses, ammonia gas, water, and air, to furnish an edible material rich in protein and vitamins. Whether the large scale cultivation of the lower types of organisms will develop a new era in human and animal nutrition can scarcely be predicted; the program is only in its initial stages. It is possible however that the new method may partially solve the problem of producing cheap protein and vitamins in countries which have not been able to provide proper foodstuffs.

This possibility should be recognized by nutritionists who must supply data relative to the food value of such a product. In this connection Hock and Fink (*Z. physiol. Chem.* **278,** *136 (1943)*; *Ibid.* **279,** *187 (1943)*) have indicated that yeast protein is not well balanced with respect to certain amino acids and must be supplemented in order to prevent symptoms of deficiency disease.

The authors were interested in the relative biologic value of proteins derived from animal sources (fish and milk) and from yeast. Growing rats were separated into three groups, each receiving the same amounts of protein nitrogen but from different sources. Group 1 was given fish meal; group 2 received condensed skimmed milk; group 3 was fed either brewers' yeast or a type of yeast which is used to convert cellulose sugar into alcohol.

All groups received the same amount of cereals (7.48 per cent wheat and 7.29 per cent rye) and the necessary amounts of salts and vitamins. The diets contained 77 to 78 per cent carbohydrate (mainly rice-starch); 2.8 to 2.9 per cent fat (mainly cod liver oil); and 9.4 per cent protein, 1.6 per cent of which was derived from cereals and 7.8 per cent from fish meal (group 1), condensed skimmed milk (group 2), or yeast (group 3).

The rats in groups 1 and 2 showed normal growth, whereas the rats in group 3 showed poor development. Moreover, a high percentage of rats in group 3 died within thirty days. Autopsy revealed widespread pathologic changes, particularly in the liver. The liver was pale but showed extensive hemorrhages and necroses, while in more chronic cases, cirrhosis was observed. Histologically, the hepatic and endothelial cells showed fatty degeneration. The liver was poor in glycogen, but the fat content was essentially normal.

The authors cite the important work of Skinner and Muller (*J. Nutrition* **19,** *333 (1940)*). These workers showed that yeast and other mold proteins were relatively poor in the amino acids which contain sulfur (cysteine, homocysteine, methionine). They also demonstrated that animals fed yeast proteins showed subnormal growth, but regained normal growth upon addition of cysteine to the diet.

The observations of Skinner and Muller led the German workers to the assumption that the growth disturbance and liver injuries which they observed in the rats fed yeast proteins were likewise due to a cystine deficiency. They were able to show that addition of cystine to the yeast protein diet corrected these conditions. The addition of l-cystine in amounts corresponding to 0.2 per cent of the total amount of food intake or about 2 per cent of the total protein intake was sufficient to give normal growth.

Later work in this country adds further evidence to show the importance of sulfur-containing amino acids for the functioning of the liver. Miller and Whipple (*J. Exp. Med.* **76,** *421 (1942)*) studied the resistance of the liver to chloroform and other poisons in normal animals and in protein depleted animals. They found that in the latter animals the liver was much more susceptible to the

injurious action of chloroform than in normal animals. Since they found that during protein depletion the sulfur content of the liver dropped more than the nitrogen content, they naturally became interested in the action of sulfur-containing amino acids on the tolerance of the liver. They found that methionine or cysteine + choline effectively protected the liver against chloroform poisoning.

Thus, an ample supply of methyl donors is as important for the liver as is a normal supply of sulfur-containing amino acids. This is confirmed by the studies of Daft, Sebrell, and Lillie (*Proc. Soc. Exp. Biol. Med.* **50,** *1* (*1942*)). In a study of the effect of choline and cystine on liver damage, they found that cystine added to a diet which produces liver cirrhosis aggravates the cirrhosis, whereas it tends to prevent hepatic hemorrhage and necrosis. Paradoxically, Earle and Victor (*J. Exp. Med.* **75,** *179* (*1942*)) found that rats fed excessively large amounts of l-cystine developed necrosis and hemorrhages in the liver.

A certain ratio between choline and cystine apparently seems to be of importance for the normal functioning of the liver. Methionine, which is methylated homocysteine, protects the liver as effectively as does a combination of choline plus cystine (or cysteine), a fact which was demonstrated by du Vigneaud, Dyer, and Kies (*J. Biol. Chem.* **130,** *325* (*1939*)). Hock and Fink conclude that since the animals fed yeast protein were cured by the addition of cystine, the diet must have contained a sufficient amount of methionine. It would appear that the yeast contained an insufficient amount of sulfur amino acids, whether cystine or methionine. Presumably methionine should be at least as effective as cystine in overcoming the sulfur deficiency, and in support of this, Jackson and Block (*J. Biol. Chem.* **98,** *465* (*1932*)) have reported that methionine, like cystine, is capable of producing normal growth in rats when added to a basal diet poor in cystine. Hock and Fink also tried feeding casein, which is known to be poor in cystine, as the main source of protein (9 per cent protein level). They observed that although the growth was not seriously affected, the same type of liver injury developed as in rats on a yeast protein diet. Addition of cystine to the casein diet protected the animals against liver damage.

It is important to determine whether increasing the amount of protein which is deficient in cystine will give rise to better growth and better protection of the liver by increasing the absolute amount of ingested cystine. It is a well known phenomenon that an increase in casein from 10 per cent to 20 per cent of the diet is sufficient for normal rat growth. The same seems to be true of mold proteins. Skinner (*J. Bact.* **28,** *95* (*1934*)) found that the mold penicillium flavoglaucum fed at a 9 per cent protein level in an otherwise complete diet supported only very poor growth, whereas at an 18 per cent protein level a much better, although still subnormal growth was obtained. Hock and Fink, on the other hand, did not find any difference in growth or in time of survival between groups receiving 9.5 and 14 per cent of protein (yeast protein). Apparently the amounts of yeast protein necessary to furnish enough cystine are very high. The minimum amount of amino acid sulfur required for young rats was found to be 14 to 16 mg. of sulfur daily. It would be of great importance to obtain values for the amount of cystine in any particular strain of yeast which has been chosen for the production of food. Although capable of synthesizing large amounts of protein from ammonia and carbohydrates, the strain, torula utilis, appears to produce proteins which are relatively poor in cystine.

Before yeast can be used as a major source of protein for any group of people, it would seem that a cheap supply of sulfur-containing amino acids must be found as a supplement. (Digests of hair might be considered toward this end.) With supplementation, yeast may take on significant importance in the food economy of the world.

EFFECT OF PYRIDOXINE ON THE NAUSEA AND VOMITING OF PREGNANCY

Pyridoxine deficiency has never been definitely recognized in man. No one knows, therefore, what its clinical manifestations might be. Physicians, however, stimulated by the knowledge that pyridoxine deficiency in animals causes changes in the blood, skin, and central nervous system, have been prompted to test the therapeutic value of pyridoxine in patients with acne and other skin diseases, with convulsive seizures, and with marked muscular weakness. The results of these trials have already been reviewed (*Nutrition Reviews* **1,** *15, 26, 157, 370 (1943)*); they have been sufficiently encouraging in patients with acne and with muscular weakness to merit further study. Three papers by two different groups of authors have appeared in the obstetrical literature, all of which claim that the nausea and vomiting of pregnancy respond more completely to pyridoxine administration than to any of the other methods of treatment tried.

The first paper by Willis *et al.* (*Am. J. Obst. Gynec.* **44,** *265 (1942)*) reported the results of treating 44 pregnant women with thiamin and 37 with pyridoxine. Relief from nausea and vomiting occurred more frequently and more completely with the use of pyridoxine than with thiamin. The pyridoxine was given either intramuscularly or intravenously in doses which varied from 50 to 1000 mg. Improvement was marked or complete in 23 patients and partial in 10; there were only four therapeutic failures. The authors make no comment about the general nutritional status of their patients; apparently none of the common signs of deficiency disease was observed.

This report led Weinstein, Mitchell, and Sustendal (*Am. J. Obst. Gynec.* **46,** *283 (1943)*) to use pyridoxine in the treatment of 32 similar patients. The vitamin was given by intramuscular injection in doses of 50 or 100 mg. three times weekly until nausea was relieved. When vomiting was severe, relief was usually not obtained until after the third or fourth injection. Fourteen of 16 pregnant women who were nauseated only in the morning were completely relieved; the remaining 2 were partially relieved. Each of 6 patients recovered completely from nausea which had been present throughout the whole day. In 3 of 4 instances in which nausea was accompanied by occasional vomiting, complete relief was obtained; in the fourth case there was but slight improvement. The authors were most impressed by the improvement shown by 6 patients in whom nausea and vomiting were so severe as to make impossible the retention of food. Nevertheless, they cautioned that pyridoxine should not be used as the only therapy, but as an "adjunct to sedation and proper instruction as to diet."

In a complementary study, Weinstein, Wohl, Mitchell, and Sustendal (*Am. J. Obst. Gynec.* **47,** *389 (1944)*) treated 78 patients with nausea and vomiting of pregnancy by giving orally 10 to 20 mg. of pyridoxine three or four times daily. Ten of the patients were vomiting so regularly that initial therapy had to be given parenterally for several days in doses of 100 mg. The use of sedatives was "restricted"; whether this means that sedatives were withheld is not clear. Relief occurred often within twenty-four to forty-eight hours. The response was considered good in seventy instances; in the remaining 8 patients relief was only partial or it became necessary to use other forms of treatment (intravenous fluids, sedation) as well. Two of the 10 patients with severe symptoms were in this latter group. Occasionally a patient who had become symptom-free discontinued taking the pyridoxine and experienced a recurrence of symptoms after two to five days. Resumption of the therapy was always followed by prompt improvement. No attempt is made to explain the action of pyridoxine in producing these results.

Evaluation of the nutritional status of the patients or of their diets is not included in any of these three reports. Clinicians have learned from bitter experience to be very cautious about therapeutic claims, particularly when use of a drug is purely empirical. Therefore, even though the results appear encouraging, further confirmation is necessary before they can be accepted without reserve. Even though future evaluation justifies the enthusiasm of the authors, caution must be exercised in accepting this effect of pyridoxine as a nutritional effect. The substance may conceivably have pharmacologic properties other than those which characterize it as a vitamin.

THE PIGMENT OF DIETARY CIRRHOSIS OF RATS

Lillie, Daft, and Sebrell (*Pub. Health Reports* **56,** *1255 (1941)*) have described the occurrence of a coarsely globular pigment in the phagocytes of cirrhotic livers of rats fed a diet low in both protein and fat. In subsequent papers these workers reported the occurrence of this pigment in liver cells, lung, spleen, lymph nodes, bone marrow, and adrenal cortex. When the basal diet was supplemented with choline, methionine, or casein, the pigment did not appear. Because of its waxy appearance and reactions, the pigment was named ceroid. Similar pigment has been reported in the cirrhotic livers of rats fed low protein-high fat diets by Blumberg and McCollum (*Science* **93,** *598 (1941)*) and by György and Goldblatt (*J. Exp. Med.* **75,** *355 (1942)*), and in the livers of rats fed low protein diets supplemented with the carcinogen, p-dimethylaminoazobenzene (Edwards and White, *J. Nat. Cancer Inst.* **2,** *157 (1941)*). When rats were fed this carcinogen together with a high protein diet no ceroid was found in the liver (Smith, Lillie, and Stohlman, *Pub. Health Reports* **58,** *304 (1943)*).

Endicott and Lillie (*Am. J. Path.* **20,** *149 (1944)*) report further observations on the properties of this pigment. Ceroid occurs in globules varying in diameter from 1 to 20 microns. These appear occasionally in liver cells but ordinarily are found in large rounded phagocytes. In moderate to marked cases numerous phagocytes form broad sheets and trabeculae which divide and encircle nodules of liver cells. In sections stained in hematoxylin and eosin, the ceroid appears as pale yellow globules. Eosin and polychrome methylene blue stain ceroid yellowish green to greenish blue. The pigment is strongly acid-fast. It gives several reactions for fat and stains brownish orange to orange-red with sudan IV. It is stained red in Mallory's stain for hemofuscin. It is negative for iron. It is not removed from paraffin sections by prolonged treatment in water, alcohol, acetone, ether, chloroform, or similar fat solvents. Other properties of the pigment are given in the paper cited.

Ceroid has shown no properties which would justify classing it with anthocyanins, sterols, carotenoids, porphyrins, or the hemoglobin derivatives. Although ceroid as previously noted gives several reactions for fat, it is not soluble in ordinary fat solvents and demonstrates staining reactions not shared by neutral fat, ordinary fatty acids, and the simpler lipoids. The available evidence suggests that it may represent a lipoid conjugated with protein as suggested by György and Goldblatt. The properties of the substance make it seem unlikely that it is hemofuscin as proposed by Blumberg and Grady (*Arch. Path.* **34,** *1035 (1942)*).

It seems reasonable to suppose that this substance arises from remnants of liver cells.

THE NUTRITION OF THE COTTON RAT

The cotton rat, Sigmodon hispidus hispidus, is finding an increasing use in experimental laboratories, despite some difficulties in breeding and handling. When Armstrong (*Internat. Bull. Econ. Med. Res. and Pub. Hyg.* **A 40,** *158 (1939)*) discovered that poliomyelitis can be transmitted to the cotton rat, the laboratory worker for the first time had a small animal useful in the study of this disease. McIntire, Schweigert, and Elvehjem (*J. Nutrition* **27,** *1 (1944)*) have studied the nutrition of this species and have made the interesting observation that in contrast to the usual laboratory species, the cotton rat requires both niacin and inositol.

Thiamin, riboflavin, pantothenic acid, pyridoxine, and choline were found to be required in approximately the same quantities by cotton rats as by white rats. In thiamin deficiency the same convulsive characteristics with polyneuritis were observed in the two species. Cotton rats on low riboflavin intakes showed no skin symptoms but were abnormally nervous and excitable. In pantothenic acid deficiency, rats of this species showed neither graying of the fur nor adrenal hemorrhages but developed a severe dermatitis. The skin over the entire body became crusted and cracked open, causing large sores. Pyridoxine deficient animals showed no symptoms other than poor growth. Preliminary experiments with choline were mentioned but not described.

Cotton rats placed on a synthetic diet free of niacin but supplemented with thiamin, riboflavin, pantothenic acid, pyridoxine, choline, and inositol grew poorly, weight gains averaging 2.9 g. per week. In some rats the mouths appeared to be slightly inflamed. Rats receiving niacin but no inositol gained on the average 3.5 g. per week and showed a loss of hair on the sides of their bodies. When the animals received both niacin and inositol, they showed no deficiency symptoms and grew more rapidly but still at a subnormal rate. A further improvement in the rate of growth resulting from the inclusion of liver extract in the diet indicates that the cotton rat needs other and unidentified growth factors, in addition to those studied.

VALUE OF CROSS SECTION DIETARY SURVEY OF CALORIC INTAKE

The study of food consumption as indicated by actual dietary records has become an important tool in the investigation of the nutrition of population groups, partly because more direct methods of appraising the nutritive state are controversial or lacking, but also because the consumption records yield information which indicates the causes of faulty nutrition when it is present and which can be used directly in planning corrective measures. To use actual food consumption as an indirect measurement of the nutritional status, the intake is calculated in terms of individual dietary essentials and compared with standards of adequacy for each essential. A convenient and widely used yardstick for such comparisons is provided by the Recommended Dietary Allowances of the Food and Nutrition Board of the National Research Council. An immediate difficulty encountered in using this or any other yardstick is the fact that a single figure, presumably for mean or average requirement, is given for each age and sex group, and there is little information available as to the normal variability of the requirement among individuals. The dietary intake varies greatly among individuals of the same age and sex, and interpretation of the ratio of intake to requirement is hazardous if variability in requirement is not taken into consideration. Furthermore, to

evaluate the ratio of intake to requirement in statistical terms of probabilities of chance occurrence of different degrees of variation from unity, the degree of error inherent in the methods of determining both the requirement and the intake must be known.

These problems are amply presented in a study of the caloric intake of high school students in New York City by Wiehl (*Milbank Memorial Fund Quart.* **22,** *5 (1944)*) in which an estimate of the caloric requirement was made for each individual. The study included 300 pupils between the ages of 11 and 18 years of a private school, and nearly 2000 pupils in a public school ranging from 13 to 18 years of age. Activity records for two days were obtained on each subject by interview, and the type of activity classified in four degrees of energy expenditure. The average basal calories per hour were estimated from the standards of Boothby, Berkson, and Dunn (*Am. J. Physiol.* **116,** *468 (1936)*), using determined height and weight to calculate surface area. The basal calories were multiplied by appropriate factors for the number of hours spent at each level of activity, with an allowance of 88 per cent of basal for sleeping hours, and an over-all addition of 13 per cent of the total made for waste and growth. The private school pupils were not very active, and had more sleep and less moderate and severe exercise than the public school pupils. Seventy-seven per cent of the boys in the private school spent from nine to twelve hours a day in sedentary occupations as compared to 35 per cent in the public school; corresponding figures for the girls were 70 and 44 per cent.

Wiehl attempts to estimate the error of this method of determining individual caloric requirement by adding to the standard deviation of the observations on which the average basal metabolic rate used in the calculations are based, the errors introduced by placing energy expenditure at four arbitrary levels of activity, and of an arbitrary allowance for waste and growth. The standard deviation, or error in the estimate of individual requirement is conservatively placed at 14 per cent. Various reports are cited to indicate the lack of agreement on standards for basal metabolism during adolescence, those used ranging from good agreement to between 4 to 18 per cent higher than others.

The most striking finding in the tabulations of the estimated requirements is the marked variation among individuals of the same age and sex. The greatest difference between individuals of the same age was, for boys, 2000 calories in the private school students, 3200 calories in the public school students; for girls, 1400 calories in the private school subjects, and 2300 calories in the public school group. With such tremendous variation among individuals of the same age and sex, it appears impossible to evaluate the adequacy of an individual diet by comparing it with an average or standard allowance.

Consideration of the mean estimated requirement for each age and sex group shows no significant change with age among the girls; the highest mean requirement level was 2557 calories among 14 year old public schoolgirls, the lowest 2320 among 17 year old private schoolgirls. In contrast, the mean requirement for boys showed a steady increase with each year from the ages of 12 to 18, with the public schoolboys 200 to 300 calories higher than the private schoolboys of the same age. Ranging these values alongside the recommended allowances of the National Research Council, it is seen that the means for all the groups of girls agree with the 2400 calory allowance for the 16 to 18 year old group, but that the recommendation of a 2800 calory allowance for 13 to 15 year old girls is not borne out. For the boys, the means for the groups between 13 to 15 years of age ranged from 300 calories below to 125 calories above the recommended allowance of 3200. However, for 16 to 18 year old boys the means of each group were from 400 to 670 calories below the

recommended standard of 3800. The results of this study do not support the higher allowances for 13 to 15 year old girls and for 16 to 18 year old boys. In these age groups, almost none of the private school pupils and less than one fifth of the public school pupils had estimated caloric requirements equal to or exceeding the recommended levels.

The daily caloric intake, calculated from two day dietary records obtained by the interview method, is analyzed in detail for the 300 private school pupils. These children were chiefly from families in a high income level, largely Jewish, and were regarded as a relatively privileged group. There was great variation among individuals of the same age and sex. The group means for boys showed a significant and steady progression with age, from 2438 calories for 11 to 12 year olds to 3235 for the 16 to 18 year group, with a mean of 2922 ± 61 calories for all boys. The group means for girls varied from 2140 to 2294 calories without a significant change with age, with a mean for all girls of 2243 ± 49 calories. When the calculated intake was expressed as the percentage of estimated calories required for each individual, the mean for the boys was 103 per cent of estimated calories needed which were supplied by the diet, for girls 96 per cent. There were no significant differences among the age groups for either sex. The variation among individuals again was great; less than one third of the pupils of either sex had a ratio of calories supplied to calories required within ± 10 per cent of 100, but 73 per cent of both boys and girls had ratios falling between 70 per cent and 130 per cent. Standard deviation was 28 per cent for boys, 25 per cent for girls. To find out how much of this variation can be attributed to errors inherent in the methods of estimating both intake and requirement, the author places the average error of an individual estimate of requirement at 14 per cent, that of the calculated diet record at 10 per cent, and arrives at a standard deviation of the ratio of 17 per cent as due to "experimental error." This would indicate that only individual records varying by at least 35 per cent from 100 could give statistically valid probability of an aberration not due to accidental error. Obviously, some individuals with ratios close to 100 per cent could be well out of caloric balance. The conclusion is inescapable that, regardless of the accuracy of the assumed errors, it is apparent that only markedly deficient diets can be identified. There is reason to consider Wiehl's estimate of inherent error as very conservative, particularly with respect to the calculated intake. Patterson and McHenry (*Canad. Public Health J.* **32,** *362 (1941)*) found a standard deviation of nearly 10 per cent in comparing determined and calculated caloric content of twenty meals in which the foods were actually weighed. The error in records where quantities are estimated must be considerably greater.

The calculated intake for the private school pupils was also compared to the estimated basal calories required per twenty-hour hours, the mean levels placing intake at 155 per cent of basal requirements for girls, 169 per cent for boys. The variation was of the same magnitude as when intake was compared to estimated total requirement and there were again no significant differences among the age groups. While this ratio is not subject to errors of estimating energy expenditure and will probably identify any diet below 140 per cent as deficient, it cannot indicate the degree of deficiency as well as the one using estimated total calories. Also it cannot indicate the relatively deficient diets for the more active child, and it gives no information regarding an excess of intake over requirement.

Direct information regarding the state of caloric nutrition of these private school pupils was obtained by comparing the weight of each individual to the standard weight for height, sex, and age. There was a definite tendency toward obesity: 26 per cent of the boys and 23 per cent of the girls were 15

per cent or more overweight, while only 1 per cent of the boys and 2 per cent of the girls were 15 per cent or more underweight. An unexpected finding was that the overweight children had calculated dietary intakes which tended to fall below the estimated caloric requirement, while the underweight group tended to eat more than their estimated requirements. Twenty-two per cent of the overweight boys and 29 per cent of the overweight girls had intake/requirement ratios below 70 per cent compared to 8 per cent and 4 per cent, respectively, with ratios above 130 per cent. Of those underweight, 8 per cent of the boys and 6 per cent of the girls had ratios below 70 per cent compared to 15 and 19 per cent with ratios above 130. Since obesity with its increased surface area tends to exaggerate the basal caloric requirements, tabulations were made for caloric intake per inch of height, which adjusts for differences due to extremes in weight but does not adjust for variations in physical activities. Again, however, this index tended to show an inverse correlation with the ratio of actual weight to standard weight. The author explains this discrepancy as due partly to "weight consciousness" in this privileged group and to attempts to control weight by diet, either self-prescribed or under medical supervision, and as partly due to the time lag between weight and appetite with the sudden changes in energy requirements during growth and adolescence.

The dietary intake data on the public school pupils, mostly from families in the low income brackets, with some on relief, were divided according to cultural background. Of these pupils, 1452 were Jewish, 302 Italian, and 219 (the majority with one or both parents foreign born) were classed as "others." The caloric intakes were calculated from one or two day consumption records obtained by interview, supplemented by household records for two days kept by the child's mother. The mean values for the boys showed slightly but no significantly higher levels in the 16 to 19 year olds compared to the 13 to 15 year age group. For the girls, values were slightly higher in the 13 to 15 year olds, the difference being significant only in the Jewish girls. Mean caloric intake was lowest in the Jewish group, 2660 for boys, 2062 for girls, next for the Italian group with 2878 and 2281 calories respectively, and highest for the others, 3034 and 2319 calories. The mean absolute caloric intake was significantly lower than that of the private school pupils, in the girls only among the 16 to 19 year old Jews, in the Jewish boys of both age groups, and the older age group of Italian boys.

However, when the ratio of intake to the estimated caloric requirement is calculated, the mean ratio for the boys of all three cultural groups was significantly below that for the private school pupils, with mean values of 82 per cent of required calories being furnished in the Jewish group, 91 per cent in the Italian group, and 92 per cent in the others. The value for Jewish girls was also significantly low with a mean ratio of 86 per cent.

The conclusions drawn from this study regarding what can and what cannot be accomplished by cross section dietary surveys of this type merit the attention of persons interested either in the conducting of such surveys or in the utilization of the data collected. Results of such surveys cannot be expected to correlate with more direct measurements of the nutritive state, in this case weight, which reflect cumulative rather than current intake. To obtain this, observation over a period of time is necessary. Furthermore, the intake should be expressed in terms of carefully estimated individual requirement; with respect to calories, this differs so much among individuals that the use of average or standard figures may be misleading. It would appear that error in estimating both intake and requirement is so great that this method will

not permit the selection of undernourished individuals. On the other hand, the means and distributions obtained do characterize grossly the situation of the group and indicate the probable incidence and degree of insufficiency, provided the requirements for the group can be determined with reasonable accuracy. Comparison of groups by statistical methods will indicate real differences and their degree, and can give valid evidence for selection of groups in need of attention and furnish a sound basis for the shaping of public policies toward nutrition. While this study deals only with the caloric status, it seems likely that similar principles can and should be used in the interpretation of data regarding other nutritive factors which are obtained by the dietary survey method.

THE RENAL PATHOLOGY OF NUTRITIONAL HYPERTENSION IN RATS

A number of reports in the literature suggest that structural abnormalities of the kidneys develop in association with deficiency of vitamin B-complex. The work of Newburgh (*Arch. Int. Med.* **24,** *359* (*1919*)) showed that an excessive intake of proteins leads to significant alterations in the kidney, but these deleterious effects were found later to be preventable by feeding an adequate supply of the vitamin B-complex (Longwell, Hill, and Lewis, *J. Nutrition* **5,** *539* (*1932*)). The vitamin B-complex protects against cystine nephrosis. "Hemorrhagic degeneration" of the kidneys has been described in choline deficiency (Griffith and Wade, *J. Biol. Chem.* **131,** *567* (*1939*)) and pantothenic acid deficiency in dogs and in rats has been found to be associated with similar changes (Schaefer, McKibbin, and Elvehjem, *J. Biol. Chem.* **143,** *321* (*1942*); Supplee, Bender, and Kahlenberg, *Endocrinology* **30,** *355* (*1942*)), although this has not been found in pigs (Wintrobe *et al.*, *Bull. Johns Hopkins Hosp.* **73,** *313* (*1943*)).

Calder in 1942 reported a rise in blood pressure in rats fed a diet deficient in the heat-stable fraction of the vitamin B-complex (*J. Exp. Med.* **76,** *1* (*1942*)). When the entire B-complex was lacking, there was a slight fall in blood pressure, but when only the heat-stable fractions were deficient, there was a rise which seemed to be reversed by restoring these factors to the diet. Partial deficiencies seemed to be followed by a higher rise in blood pressure than were complete deficiencies. It is curious that an excessive intake of the heat-stable fractions of the vitamin B-complex did not prevent entirely the rise of pressure if the diet was otherwise deficient. Under the latter conditions, however, the rise in pressure seemed to be slower and less marked than in those animals with a deficiency of the heat-stable fraction of the vitamin B-complex.

The blood pressure of the animals was measured in most instances by the indirect method of Williams, Harrison, and Grollman (*J. Clin. Invest.* **18,** *373* (*1939*)). The method is open to some criticism and the records are not entirely convincing. However, direct blood pressure determinations, made by inserting a cannula into the abdominal aorta, tended to confirm the indirect measurements since the blood pressures of 10 deficient rats were higher than those of the same number of well nourished rats.

In a later report (*J. Exp. Med.* **79,** *215* (*1944*)) Calder describes the renal pathology in the above mentioned animals. The differences in the pathologic anatomy of the kidneys of animals in the various groups were striking. Without exception the kidneys of rats which had received liver extract or brewers' yeast were entirely normal on gross examination as well as microscopically. Only in a few instances did several of the large interlobar arteries show some thickening of their walls and narrowing of their lumens. When this occurred the process was confined solely to the large arteries.

There appeared to be no interference with blood flow through the vessels and infarcts of large areas of kidney substance were not observed.

In contrast, distinct changes were found in the kidneys of rats receiving autoclaved yeast in amounts of either 2.5 or 5.0 per cent of the diet by weight. (All animals received daily supplements of thiamin chloride.) The kidneys from the animals receiving 5 per cent of autoclaved yeast presented a fine granular surface. Specimens from the animals which had received 2.5 per cent of autoclaved yeast showed a rather extensive subcapsular accumulation of blood, together with microscopic areas of hemorrhagic infiltration in the parenchymal tissue. Numerous vessels, which by size and location were presumably afferent arterioles, showed conspicuous degenerative changes consisting of subendothelial hyaline deposits irregularly disposed circumferentially. These deposits occurred at an appreciable distance from the glomerulus itself, that part of the arteriole lying in the tuft stem being spared in every instance. In their course through the cortex the small interlobular arteries displayed the thickening of their walls and encroachment on vascular lumen characteristic of arteriolosclerosis. The changes in these arteries involved both the intima and the media. At times the lumens were almost completely obliterated. Small streaklike areas of ischemic atrophy were striking features in both cortex and medulla. The primary pathologic change seemed to be sclerosis of the afferent arterioles and of the interlobular arteries. The glomeruli showed lesions like those described as being typical of essential hypertension. In many of the tufts there was an increase in the thickness of the capillary basement membrane. Accompanying this change the component loops of the tuft were reduced in number with resultant simplification of the glomerular pattern. In no instance were the pathologic changes as severe as seen in advanced nephrosclerosis in man but they were similar in character. The principal difference which was noted lay in the occurrence of areas of ischemic atrophy in the renal medulla.

It is difficult to evaluate these interesting observations at this stage. It is intriguing to speculate, nevertheless, about the possibility that a mechanism for the development of hypertension is due to interference with oxidation in the kidney, not only by disturbance in circulation as the current trend in renal research indicates, but by impairment of enzyme systems. Such an impairment might lead to accumulation of an intermediate contributing to the hypertension syndrome. The renal changes described by Calder would, in this concept, be the consequence of hypertension.

TETANY AND MAGNESIUM DEFICIENCY

The induction of tetany in rats and dogs by feeding them a diet free of magnesium was reported more than a decade ago by Kruse, Orent, and McCollum (*J. Biol. Chem.* **96,** *519 (1932)*). These workers also cited observations by Sjollema and Seekles in which severe symptoms of tetany were described in calves reared on whole milk, which is low in magnesium. Low values for plasma magnesium were observed in these calves as well as in cattle suffering from "grass tetany." The development of tetany in man in association with low plasma magnesium has not been clearly demonstrated. It is true that Denis and Talbot (*Am. J. Dis. Child.* **21,** *29 (1921)*) reported several cases of tetany in patients who showed low values for plasma magnesium, and Hirshfelder and Haury (*J. Am. Med. Assn.* **102,** *1138 (1934)*) made similar observations, but few clinical

data were given in their reports and it is not certain that better known causes of tetany in man were ruled out.

Miller (*Am. J. Dis. Child.* **67,** *117 (1944)*) describes a well-studied case of tetany in which the plasma magnesium was low. The child was first observed to have repeated convulsions at the age of 7 months. Enlargement of the thymus was suspected to be the cause of the symptoms at that time, but roentgen irradiation was ineffective in stopping the cyanotic attacks. The convulsions occurred almost daily, lasted three or four minutes, and were characterized by cyanosis, tonus, and clonus. The blood plasma at this time contained 9 mg. of calcium per 100 ml. The convulsions gradually became less frequent, but at the age of 3 years attacks of dizziness became prominent. At 3½ years a limp in the left leg developed and examination revealed the typical picture of osteochondrosis of the capital epiphysis of the femur (Legg-Perthes' disease). The plasma calcium was 12.9 mg. The course of the Legg-Perthes' disease followed the usual sequence of epiphyseal absorption, flattening, and then slow regeneration. At the age of 6 the boy was generally well except for a tremor, first noted at 7 months of age, which now interfered with his learning to write legibly. He had not had a frank convulsion since he was 1 year of age.

The patient was seen by Miller for the first time at the age of 6 when, following treatment for malaria, the child began to complain of cramps in the calf of the right leg. In a short time the child developed typical tetany. The hands were held in the "obstetric" position and the feet were in the extended position of carpopedal spasm. The blood calcium, dextrose, and carbon dioxide-combining power were normal. Treatment with ammonium chloride and calcium gluconate was not effective but the pain and spasm eventually subsided after a period of forty-eight hours. After the attack the plasma magnesium was found to be 1.7 mg. and the phosphorus 3.3 mg. per cent.

Since the plasma magnesium was at the lower level of what has been regarded as normal, the patient was given 0.3 g. of magnesium sulfate to take three times a day by mouth. The symptomatic improvement which followed is described as striking. The tremor and attacks of dizziness disappeared and the patient's writing improved considerably. The reactions of the muscles to electric stimulation showed substantial improvement.

Even though there was no evidence that the child was suffering from one of the well known causes of tetany, the claim that the tetany was caused by a low plasma magnesium level was still unconvincing up to this point. Fortunately for scientific reasons and unfortunately for the patient, he was taken on a trip and the prescribed magnesium was left at home. After about a week without the medicine, the tremor and severe cramps returned. On examination positive Trousseau signs and a positive Chvostek reaction were obtained. The plasma magnesium content, measured for the first time during an attack of tetany, was found to be 0.6 mg. per 100 ml. The plasma calcium at this time was 11.2 and the plasma phosphorus 2.2 mg. The plasma magnesium was rechecked and was found to be the same. Magnesium sulfate was prescribed and the previously described benefits were observed once more. The blood magnesium after two weeks of therapy was 2.6 mg.

One case such as this does not prove the author's thesis that low plasma magnesium may be associated in man, as in the rat and the dog, with the development of tetany. It must be admitted, however, that the evidence presented is impressive and physicians should be on the lookout for other cases of this kind. The author raises the interesting question whether osteochondrosis of the capital epiphysis of the femur might in some way have been related to the low magnesium level.

NOTES

Livestock Feed Supplies and Needs

The Feed Industry Council (J. A. McConnell, Cooperative G. L. F. Exchange, Ithaca, N. Y., President) was organized in December, 1942, with a twofold objective: (1) to serve as a fact-finding body making investigations as to feed supplies and needs, and (2) to work with government and industry in developing programs that will result in the most efficient usage of all feedstuffs.

The most recent report issued by the Feed Industry Council entitled "Feed Supplies and Needs for the Current Feeding Year" summarizes a survey of feed supplies and needs by the livestock industry, for the feeding year ending September 30, 1944. This survey was conducted by a group of agricultural college and experiment station workers representing administration, nutrition, animal and poultry husbandry, and economics. Latest government reports on feed supplies, food goals, and livestock numbers, and published data on previous utilization of the feed supply served as the basis on which the calculations in the report of this committee were made.

The results of this survey indicate that there will be a deficit of 18 million tons of concentrate feeds when the estimated needs of the livestock industry are balanced against the estimated supplies for the year ending September 30, 1944. This finding must be carefully interpreted since feed supply in relation to the livestock population is constantly and rapidly shifting from day to day, and month to month, as the result of changing crop conditions, and decisions on the part of government, industry, and farmers as to important feed supplies, rates of feeding and expansion, or reduction of livestock numbers on farms.

The paramount problem is to close this 18 million ton gap in such a manner that production of foods essential for the war effort is maintained at the highest possible level with the feed that is available. This gap may be closed in several ways: (1) The rate of feeding which has been going on may slow down as the effects of the feed gap take hold; (2) Livestock and poultry numbers may be reduced; and (3) The government with its wartime powers may authorize the use of domestic wheat and the importation of grains, proteins, and molasses from abroad. The extent to which each of these possibilities materializes will determine whether the greatest possible amounts of the kinds of food needed for the war effort are to be obtained.

Thiamin in Potatoes

Potatoes often constitute the backbone of the common American or European dinner. Because of the high starch content of the potato, it is a concentrated source of calories and its crop yield is greater per acre than that of any other starch food. This food is now becoming recognized as an important source of dietary essentials other than carbohydrate. Potatoes may contribute greatly to the daily supply of ascorbic acid by virtue of the quantity consumed rather than because of a high concentration of the vitamin. Meikeljohn (*Biochem. J.* **37**, *349 (1943)*) reveals that the potato may also represent an important source of dietary thiamin.

Using the Phycomyces method for estimating thiamin, Meikeljohn studied the thiamin content of tubers and different parts of the plant throughout the growing season, the distribution of thiamin in different parts of the plant, and the effect of storage on the thiamin content. It was found that the thiamin content of tubers increased continuously up to the time of lifting (September). At this time the thiamin content of the tubers (Majestic variety) was about 140 micrograms per 100 g. The thiamin was found to be concentrated in the center of the

tuber rather than the skin, which is also true with ascorbic acid.

Upon storage the thiamin content of the tubers fell somewhat during the winter and more noticeably in the spring. The latter loss appeared to be related to sprouting since the white sprouts were found to have a higher thiamin content than the tubers.

On the basis of 140 micrograms per 100 g., 12 ounces of potatoes, if properly cooked in their skins, would provide 470 micrograms of thiamin. Such a serving of potatoes therefore represents at least one third of the suggested daily allowance of thiamin.

Nutrition Pamphlets

The following pamphlets issued by the Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U. S. Department of Agriculture, Washington, D. C., are available, free of charge, for those who may be interested in them: Family Food Plans for Good Nutrition, AWI-78; Vitamins from Farm to You, AWI-2; Fight Food Waste in the Home, AWI-3; National Wartime Nutrition Guide, NFC-4; Meat for Thrifty Meals, Farmers' Bul. 1908; Poultry Cooking, Farmers' Bul. 1888; Fats in Wartime Meals, AWI-34; Cooking with Soya Flour and Grits, AWI-73; Homemade Bread, Cake, and Pastry, Farmers' Bul. 1775; Green Vegetables in Wartime Meals, AWI-54; Root Vegetables in Wartime Meals, AWI-39; Dried Beans and Peas in Wartime Meals, AWI-47; Potatoes in Low-Cost Meals (unnumbered); Cheese in Your Meals, AWI-16; Honey and Some of Its Uses, Leaflet 113; School Lunch Recipes, miscellaneous publication-537. In addition the Bureau of Human Nutrition and Home Economics has prepared a series of charts dealing with various phases of nutrition. These are on sale for a small sum by the Superintendent of Documents, Government Printing Office, Washington, D. C. The charts are designed primarily for group use and at present these four series are available: Soya Flour and Grits; Get the Good from your Food; Fight Food Waste; and Nutrition Charts.

"A" Awards

A grateful nation bestows the symbol "A"—the "A" of achievement—for outstanding performance in the production of food. This "A" award is presented by the War Food Administration, for food production, to honor the farm families of those counties which have made outstanding production records. For food processing, it is presented to outstanding plants.

Until today, the coveted "A" award for outstanding achievement in food processing has been limited to certain kinds of seasonally-operated plants. But from today forward, the Achievement "A" will be the goal of all food processors, large and small, seasonal and year 'round. The only exceptions will be certain plants which qualify for the Army and Navy "E" Award. The Army and Navy will continue to confer the "E" upon these. These two awards—the "A" and the "E," will symbolize the gratitude of all America to the food industry for its valiant efforts to make food fight for freedom all over the world. (From a radio address by Marvin Jones, War Food Administrator.)

Vitamin and Mineral Values of Foods

The third compilation of recent data on vitamin and mineral values of foods has been published by a Subcommittee of the Diet Therapy Section of the American Dietetic Association under the chairmanship of Dr. Ruth Cowan Clouse (*J. Am. Dietet. Assn.* **19,** *746 (1943)*). Sixty-two articles, covering mainly the period from January to June 1943 and including the first progress reports of the National Cooperative Project on the "Conservation of the Nutritive Value of Food" now under way in a number of State Agricultural Experiment Stations, have been reviewed in this report. Reprints are available from the American Dietetic Association, 620 N. Michigan Ave., Chicago 11, at a cost of 20 cents each.

THE NUTRITION FOUNDATION

The Nutrition Foundation was organized by food and related manufacturers to develop and support a comprehensive research and educational program in the science of nutrition. It functions chiefly through grants in support of research in university centers where there are strong graduate schools in the basic sciences. Nutritional problems of immediate importance in relation to the war emergency receive special consideration.

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